PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

MODTAGET
13 APR. 2004 PCT

To:

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Patent Department
Smedeland 26B
DK-2600 Glostrup
DANEMARK

WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	07.04.2004
Applicant's or agent's file reference 022-2003 WO1	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/DK 03/00463	02.07.2003	04.07.2002

International Patent Classification (IPC) or both national classification and IPC
C07K14/575

Applicant
ZEALAND PHARMA A/S et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☐	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 04.11.2004

Name and mailing address of the international preliminary examining authority:

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I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-43 as originally filed

Claims, Numbers

1-78 as originally filed

Drawings, Sheets

1/8-8/8 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-78 (YES)
Inventive step (IS)	Claims	1-78 (YES)
Industrial applicability (IA)	Claims	1-78 (?)

2. Citations and explanations

see separate sheet

Additional remarks to section V:

1. Novelty and Inventive step (Article 33(2) and (3) PCT)

1.1 The present application discloses a method for the treatment of diabetes comprising administering GLP-1 or a related molecule, characterized in that the amount and timing of administration includes a so-called 'drug-holiday' during which said GLP-1 or related molecule is reduced or absent. Said method appears to be based on the finding that the GLP-1 analog (compound 1), when administered for 40 days, has a sustained effect after the administration of the compound is stopped (Figures 5-8).

1.2 The documents mentioned in this written opinion are numbered as in the International Search Report (ISR), i.e. D1 corresponds to the first document of the ISR etc.

1.3 The GLP-1 and related molecules are known in the art and so is their use in the treatment of diabetes (all cited documents). The compound used in the examples of the present application (designated compound 1) seems to correspond to the compound represented by SEQ ID NO: 93 in document D4 (designated compound 2 in D4) and is thus also known in the art. None of the cited prior art documents discloses the concept of 'drug holidays', i.e. of reducing/stopping the administration of the GLP-1 drug for a certain time interval during the therapy. None of the cited documents discloses the sustained effect of GLP-1 on glucose metabolism and pancreatic expression of insulin. Therefore the concept of reducing/abolishing administration of the compound at intervals ('drug holidays') appears to be inventive.

1.4 In the present application the effect of compound 1 is shown to last for 40 days after stopping administration of the compound (Figures 5-8). It is noted, however, that in D4 the effect of compound 2 (corresponding to compound 1 of the present application) is shown to last for about 18 hours (see Figure 8 and p. 60). Therefore it is questioned whether the subject matter of the present claims is enabled over the entire breadth covered by the claims. It seems that the timing of drug administration/reduction is essential to achieving the sustained effect of the compound. Furthermore, due to the known instability of GLP-1 (see e.g.

documents D1, D4, D9, D10) it is questioned wether said sustained effect can be achieved with any GLP-1 analog or with GLP-1 itself. Thus it appears that the present claims lack clarity under Article 6 PCT in that the essential technical features (compound, amount and timing of administration) are not clearly defined in the claims.

clarity

2. Industrial applicability (Article 33(4) PCT)

2.1 The subject matter of claims 1-39 relates to methods of treatment of the human or animal body and is thus excluded from examination by Article 34(4)(a)(i) PCT in combination with Rule 67(iv) PCT. For the assessment of these claims on the question whether they are industrially applicable, no unified criteria exist in PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment. The applicant is already informed that in the case of a European application, claims 1-39 are not allowable because 'methods of treatment of human or animal body by surgery or by therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application'.

2.2 With regard to the subject matter of claims 40-78, in the case of a European application it is not clear, in view of the present jurisdiction, whether the feature of 'amount and timing of administration' is to be considered a non-commercial and non-industrial medical activity, excluded by the EPC, or whether it could be considered to represent a further medical indication from which novelty could be derived. This question is deferred to the possible European phase.